Moss, Bernard 2018

Dr. Bernard Moss Oral History

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This is an interview with Dr Bernard Moss on June 25th, 2018, at the National Institutes of Health (NIH) about his career in the National Institute of Allergy and Infectious Diseases (NIAID). The interviewer is Dr. Victoria Harden, the Founding Director, Emerita, of the Office of NIH History and Stetten Museum.

Harden: Dr Moss, would you state your name, and that you're aware that this is being recorded, and that you give permission for the recording?

Moss: My name is Bernard Moss, and I'm aware of the recording.

Harden: Thank you. You were born on July 26th, 1937, the younger son in your family. Would you describe your childhood and your education through high school, especially noting anyone or any experience that helped direct you towards a career in research?

Moss: I was born in Brooklyn, New York. My family was a close one. My grandparents lived in the same apartment building and my uncles and aunts lived within walking distance. I attended a public elementary school, which was just across the street. I recall that I was more interested in outside activities and sports. I liked to read, but I didn't particularly want to read what the teachers prescribed. I remember that getting a library card was exciting. I was able to walk to the library and pick out books myself. Despite the fact that I was not terribly interested in the classroom, I scored high in testing. For that reason, I went through a gifted program, called the SP system in New York City. What it did was to compress three years into two.

Harden: This was elementary school or high school?

Moss: Junior high school and the first year of high school were combined. You asked me whether any teachers were particularly stimulating. I have to say not that I particularly recall. Through junior high and high school, I did not find the teachers very stimulating, and my grades were mediocre until the last year of high school. Then I decided that I could really do well if I wanted to. In my last year, I got all As and the award in chemistry, which was a departure from everything else in the past.

My parents and my family encouraged me to become a physician. My parents were immigrants. My mother's family came to America after the first world war from what would now be the Ukraine. There was a lot of persecution of Jews there, and my mother told stories of atrocities. My father's family came from Romania, although he was born in England on the way here. My family had not engaged in higher education, and becoming a physician was a highly respected occupational goal.

Physicians were independent, and I thought that was a worthy occupation to prepare for.

I went to New York University (NYU), partly because it was familiar and enabled me to live at home. I decided to continue the studious attitude I had in my last year of high school. In fact, I got all As throughout college.

Harden: In your *Journal of Biological Chemistry* (*JBC)* article that you remember reading Sinclair Lewis's *Arrowsmith*. I presume you also read Paul de Kruif's *Microbe Hunters*. Did these books give you the idea that a career in research might be interesting?

Moss: Yes. As I said, I did read Sinclair Lewis's *Arrowsmith*. It enlarged the vista of what a physician could be. I must say, though, that the books I most enjoyed were adventure books. *White Fang*, by Jack London; *The Last of the Mohicans*, by James Fenimore Cooper—books like that.

Harden: Let’s go back to your college years at New York University. You enrolled in 1954, and apparently completed your undergraduate work in three years, correct?

Moss: That's correct—it was actually 3 ½ years as I graduated from high school 6 months early. The acceptance to start in mid-year and accelerate the graduation date was another reason why I chose NYU.

Harden: Would you talk about who might've inspired you at this point?

Moss: In my last year at NYU, I took a cell biology course. It was given by Paul Gross [Dr. Paul R. Gross], and it was the most interesting subject I had in college. He was a very good speaker and excited me about the inner workings of the cell. I had the opportunity to do an honors program, which introduced me to laboratory research. Dr. Gross had a small lab where I isolated enzymes from rat liver tissue. I enjoyed the thrill of seeing new results. After this experience, I began thinking seriously about a research career, but by that time I had already applied to medical schools. I thought of switching to a PhD program, but I was already committed to a medical school track.

The medical school that I chose was NYU, mainly because it had a very strong research program and again allowed me to commute, which was a substantial cost saving for my family. I really enjoyed my first year in medical school, except for anatomy. Microbiology, biochemistry, physiology were all very interesting to me. I had an opportunity to take an elective, and I chose the biochemistry department with Robert Chambers [Dr. Robert W. Chambers]. He was a biochemist, really an organic chemist. He showed me how to do research, how to keep a notebook, how to record every single thing. When I would weigh something, I had to put in my notebook the numbers on the scale, if there was a tare, I had to put that down, everything. It was good discipline for further research. I spent two electives in his lab and was an author on one paper.

The last two years of medical school were based largely in the clinic at Bellevue Hospital in New York City. Belleview is a public hospital and was understaffed; for that reason the medical students had more opportunities to interact with the patients, and to do many procedures. I remember how I learned to draw blood. I was in the prison ward. This was a ward with drug addicts, mostly. It was a drug addict who taught me how to draw blood. He knew I was a medical student that probably had never done it, so he said, "Look, I'm not gonna let you destroy the last vein I have. I'm gonna show you how to do it," and he did.

Harden: A lot of people who spent clinical years at Bellevue or interned there praise it as having given them the opportunity to see so many different diseases that they might not have seen in other hospitals. Do you think that way also?

Moss: Yes. There were emergencies all the time. People would arrive with a variety of diseases that required immediate attention. However, many of the patients on the wards had chronic diseases, and I found that their care was depressing. That partly discouraged me from applying for a medical internship, but in my last year I decided on pediatrics. I did that for a number of reasons. Frankly, I enjoyed working with children more than with adults. In addition, I thought that if I decided to do clinical research, infectious diseases might be a fruitful area, and genetic diseases also— both had a high incidence in pediatric patients. So, I applied for a pediatric internship. The two hospitals I was interested in were Children's Hospital in Boston, which is affiliated with Harvard Medical School, and Johns Hopkins, because they both had very good academic ratings. I remember the interview I had with the head of endocrinology, John Crigler [Dr. John Fielding Crigler] at Children’s Hospital. He made a very positive impression and really encouraged me to continue on a research career.

There was a matching system in which the medical students would rank the order of the places that they wanted to go to, and the hospitals would rank the order of medical students they wanted to make offers to. I was ecstatic when my first choice matched with Children's.

Harden: In addition, you got married on Christmas Day 1960 during your last clinical year. Had you known your wife before this time, or did you meet her while you were in medical school?

Moss: I met my wife while in medical school. It was through friends. We dated for a couple of years and were engaged a year before we married. Originally, we were going to marry when I graduated from medical school, but in thinking of the hectic life of an intern I thought it would be better to marry before then. Christmas day, of course, was a day off for me. In fact, I had a week off. We married on Christmas Day and that evening we took a flight to Puerto Rico for a week-long honeymoon.

Harden: An actual honeymoon for a medical student during his clinical years! She also must be very bright and hardworking, because she apparently finished her undergraduate work in three years. You said she was twenty when you moved to Boston, and she got a job right away.

Moss: Toby was teaching for a year before we moved. I think she graduated from college when she was 18 or 19.

Harden: Wow.

Moss: We didn't know each other when we were children, as she lived in a different neighborhood in Brooklyn, but she also went through the accelerated SP program.

Harden: She taught second grade. You described her as a charismatic teacher.

Moss: Yes – she would frequently dress up as literary characters to entertain and teach. Toby actually taught in the elementary school that I went to. She worked with some of the teachers who had taught me, which was weird.

So, then we went up to Boston, and rented a small apartment near the hospital. Toby quickly got a teaching job, and I started my internship. At that time, interns were expected to work every day and every other night. That meant thirty-six hours or more without a break. We had a room in the hospital in which to sleep if we had a chance. It was exhilarating but at the same time daunting because we were working with small children.

A baby is so tiny, and one of the most perilous conditions was severe diarrhea in an infant. We had to give IVs and to figure out how much fluid to give the babies. It had to be right. The margin of error was small. We also had to make a quick and accurate diagnosis when a baby came in with high fever and possible meningitis.

One of the rotations I had was in the Jimmy Fund building, which housed cancer treatment for children. That rotation was traumatic for everybody who went through there, because there weren't any cures. It was a time when cancer drugs were being tested. The goal of these chemotherapies was to work out the proper dose for pediatric patients. The children rarely survived. Their parents had rooms on the floor above, so whenever a crisis occurred you were working with parents there as well as with the children. It was very difficult. The year after I was there, an intern committed suicide. It had been an internship rotation, but after that, they changed it to a residency so that people with more experience would work with these patients.

Harden: When you finished your internship and after all your medical training, your heart was apparently still in the laboratory. I always ask research physicians, why did you want to go into laboratory research as opposed to private practice or public health?

Moss: Well, research and private practice are very different things. At this time, I wanted to understand biological processes on a fundamental level. I was interested in causes of disease, but even more, of life itself. I had decided that if I was going to do research, I had to have the best training. I felt that when I was in college, I didn't take enough hard science courses. What I wanted to do after internship was to enroll in a PhD program so that I would be able to take mathematics and chemistry courses that are not usually part of postdoctoral training programs. I wanted to have the best background possible.

In trying to determine how to do this, I decided to speak to Louis Thomas [Dr. Louis Thomas], who was a very well-known educator, philosopher, and importantly for me, chairman of medicine at NYU, my alma mater. Although I had no previous direct interactions with Dr. Thomas, I made an appointment to speak with him. I wanted his advice. He asked me what I wanted to do, and then, near the end of our conversation, he said that he had a grant from NIH to train physicians in basic sciences. He offered to support my further training. Amazingly, without committees, and no formal application, he just offered it to me. I told him, however, that I would not accept if this was training to go back to NYU medicine, that I wanted freedom to pursue my goals. He said there were no strings attached. This was very helpful because if I went into a PhD program I would have a graduate fellowship, which at the time was about $2,000 a year. The training grant provided a postdoctoral stipend, which was $6,000 a year. That amount of money meant that we were able to afford having children during my graduate work. It also gave me a lot of independence in selecting a program.

Jack Buchanan [Dr. John M. Buchanan], who was chairman of biochemistry at MIT, allowed me to take the courses that I wanted. He said, "We'll count your medical school as electives in biology." So, I took mathematics, physical chemistry, and advanced chemistry. I felt that I then had the background that I needed for my career.

Harden: Why did you choose MIT instead of Harvard?

Moss: While I was at Children's Hospital in Boston, I looked at the programs at Harvard Medical School, Harvard College in Cambridge, and MIT. I liked MIT because it had a biology department with a biochemistry division.

The whole department was on three floors of the building. I liked the idea of a comprehensive education. Biochemistry was the focus, but I was able to interact with students who were in other areas of biology. I felt that was an advantage. At Harvard there were different buildings for different disciplines, and I felt this was not really going to work as well for me. The other part was the rigor of the mathematics and chemistry courses at MIT. I was perhaps a masochist in choosing MIT for this reason.

Harden: I assume that the fellowship you got also served as a deferment from the draft at this point, the doctor draft.

Moss: The fellowship itself didn't provide the deferment; enrolling in a degree program did. At the time there was not a general draft, but there was a doctor's draft. However, enrolling in a degree program with a training grant allowed a four-year deferment from the doctor draft. That was a second reason for enrolling in a graduate degree program. The first reason was to take more formal science courses, which I would not be able to do as a postdoctoral fellow. But the other important reason was that I had a deferment.

Harden: When you arrived at MIT, you must have found yourself immersed in the exciting period when biochemical work on the genetic code was being done, and genetics and molecular biology were all ramping up. It must've been a very exciting time. Would you talk about what you saw going on, and whom you interacted with?

Moss: Right. The year before I entered MIT, there was a very important publication by Brenner, Jacob and Meselson [Drs. Sydney Brenner, François Jacob, Matthew Meselson], which described RNA as being the intermediate between DNA and proteins. Students now probably think that this was known for a century, but it was not. It was something that was found in bacteria, and what was exciting to me was to try to transfer these concepts to eukaryotic cells.

I was interested in working on a topic on the regulation of gene expression. I decided to work in Vernon Ingram's laboratory [Dr. Vernon Martin Ingram]. Ingram was well-known because he described the first disease with a molecular cause, sickle cell anemia. He showed that a single amino acid mutation was the cause of the disease. When I spoke with Dr. Ingram, he suggested that I work on the developmental biology of hemoglobin. It was known that in humans there's a fetal hemoglobin, and there's an adult hemoglobin. However, the mechanism of the switch in hemoglobins was unknown. The question was: Is there a similar switch in hemoglobins of animals that can be studied in the laboratory? Dr. Ingram suggested that I work on either chick embryos or frogs. I decided to work on frogs because it was known that if you give thyroid hormone to a tadpole, it will metamorphose into a frog. You can do that in the laboratory.

I kept the tadpoles in plastic containers and added thyroid hormone to the water. Then every few days I would take a sample of blood and examine the hemoglobin by a technique called electrophoresis, in which the proteins in the sample are separated. I was able to show that hemoglobin was different in the tadpole and the frog so that, like humans, there was a switch. Then I injected the tadpoles with radioactive amino acids and iron in order to follow the switch as it occurred. I found that tadpole hemoglobin stopped being made within a week. Then there was a quiescent period of a day or two, and then frog hemoglobin started to be made. Furthermore, tadpole red cells were made in one part of the body, and frog red cells were made in another. What the hormone was doing was suppressing the reproduction of one line of cells, and stimulating another.

Although this was interesting, it was not really what I was looking for. I was looking to see what had been shown in bacteria, in which in a single cell there is a switch in gene expression. The hemoglobin switch was far more complicated than that. But it was an interesting result, and I learned a great deal in Ingram's laboratory, mostly protein chemistry. I learned how to purify proteins, how to analyze proteins. Importantly, Ingram also had an unconventional philosophy of education for PhD students. He said that a PhD is a training for independence, and therefore he would not work very closely with his students.

Harden: He was a hands-off mentor.

Moss: He was a hands-off mentor. I don't know whether it was a rationalization for remaining aloof, or it was all his philosophy of education. But it was good for me anyway. We discussed the plan, and then he said that when I obtained some results in a couple of months I should talk to him again. At that time, Ingram was working at the bench himself with the goal of being the first to sequence a transfer RNA. He worked every day with two technicians and didn't spend very much time with students. There were a few other students also in the lab. Unfortunately, Dr. Ingram lost the race to another investigator (Dr. Robert W. Holley). They were both working on the same alanyl transfer RNA.

Harden: Did his hands-off mentoring style transfer to you when you had graduate students and postdocs of your own? Did you think the hands-off style was a good thing, something you continued?

Moss: No, I did not have the same hands-off style, but I think that working independently worked out well for me for a couple of reasons. One, I mentioned earlier that when I was in medical school I worked with Bob Chambers. He was a hands-on mentor. I had to show him my notebooks every week. I had already had that training by the time I got to Vernon’s lab. Second, I was more mature than any of the other graduate students there. I had been to medical school and internship. I was able to take responsibility, and I had no fear of doing new things. Being an intern is doing new things all the time. So, Vernon’s hands-off approach, for me, was just right.

Harden: In the spring of 1966, you got a letter from the government saying that your military deferment would soon end, and would you kindly register for the draft. This changed a part of your career. Would you talk about this and how this brought you to the NIH?

Moss: I had already been at MIT nearly four years, working on tadpoles and frogs, which did not enhance my clinical abilities. I thought that it would be best for me to continue in research without interruption. I knew that I could serve my two-year military obligation in the Public Health Service. I flew down to NIH, and I had a few interviews set up with individuals in different programs. I didn't go through the clinical program, or through any kind of a training program that the NIH had. One, it would've been too late in the year to apply, and also I already had more knowledge of what I wanted to do at that point.

One of the labs that I interviewed with was headed by Norman Salzman [Dr. Norman P. Salzman]. Actually, although it was mainly a virology lab, one of the projects he was working on was the isolation of chromosomes. My interest was in developmental biology and gene regulation, so I thought that the isolation of chromosomes would be a useful technique for localization of genes. When I arrived at NIH though, Norman had stopped working on that project.

He suggested I work instead on vaccinia virus. Nobody in his lab was working on the virus at the time. Norman had worked with vaccinia virus, but then he decided to work on a simpler virus, polyomavirus. So, I agreed to begin working on vaccinia virus. I knew a little bit about poxviruses because of a coincidence. When I was taking an exam at MIT, there was a library question on poxvirus gene expression. Very little was known mechanistically at that time, but it was recognized that poxvirus gene expression was regulated. There was an early phase and a late phase. I thought that this fit in with my ideas of trying to understand gene expression in the eukaryotic system. Although viruses are not eukaryotes, they replicate in the cell.

Harden: Before we get into your research, tell me who was in Dr. Salzman's lab when you arrived. Who were your colleagues?

Moss: That's a very good question, because the Salzman lab was a unique place. It had been Harry Eagle's laboratory [Dr. Harry Eagle] before he left for Albert Einstein College of Medicine. Harry Eagle defined the conditions for growing human cells, and animal cells in general, in tissue culture. He defined the amino acids, the vitamins, everything that had to be there. That made it possible to grow animal cells in large cultures. Before that, virologists usually worked with small tubes of primary cells that they obtained from animals. After Harry's work, virology with human and animal cells became more like working with bacteria. We could grow the animal cells, the human cells, in six-liter vats. With that number of cells, you can do many more types of experiments.

I had come to the best laboratory that I could have for the kind of work that I wanted to do. At that time, there were no commercial sources of materials to grow viruses in cell culture. Although Harry Eagle himself had moved, his technicians were still there. They would make the medium. They would go to a farm nearby, and bleed the horses, and bring the serum, because you have to grow cells in animal serum. All of that was provided on a large scale. Although I didn't have a personal technician, I had access to all the reagents that I needed as well as the way of thinking about viruses and cells necessary to do biochemistry on them.

Norman had worked on the biochemistry of poxviruses, and then papilloma virus. Aaron Shatkin [Dr. Aaron J. Shatkin] came to the NIH several years before me. He had worked with Norman. Michael Bishop [Dr. J. Michael Bishop] was there at the time. He gave me, as I remember, a five-minute course in cell culture. Everybody worked pretty independently there. Jim Rose [Dr. James A. Rose] worked on parvoviruses. Lois Salzman [Dr. Lois Salzman] also worked on parvoviruses. Michael Bishop worked on poliovirus and Aaron Shatkin on reovirus. It was not a large lab and people interacted very well.

Harden: I understand that after you got to NIH, you finished your PhD dissertation on nights and weekends. That must've been a busy time.

Moss: It was a very busy time.

Harden: Let's go back to your research. You had planned to work on the isolation of mammalian chromosomes, but Dr. Salzman redirected you to working on vaccinia virus. I find it interesting that you, like so many people, “backed into” your life's work, because after you started work on vaccinia virus, you continued the research for your entire career. But I absolutely must ask you one more question before we get into the vaccinia research. Are viruses alive, and what is the definition of life these days?

Moss: I think that the question, “Are viruses alive?” is a semantic one. We know what viruses can do. If you want to call that life, feel free to. Probably the best definition if you want to separate life forms from other biological forms, right now the difference would lie in whether the biological form has all of the capabilities to make proteins. Viruses don't have ribosomes, which are the machinery for making proteins. Viruses cannot make proteins by themselves. You can use that as a biochemical definition, if you want to distinguish life from non-life at this time.

Harden: That's a very interesting definition.

Moss: But I think in evolutionary terms, life existed before ribosomes. Exactly how viruses and cells evolved, and which evolved first or simultaneously is a matter of discussion now.

Harden: Back to vaccinia. You began to work on vaccinia using biochemical techniques. You wanted to know viral genes turn on and off. Walk me through some of this early work that you were doing.

Moss: I was working with a very large virus. At that time, conventional wisdom said that you should work with the smallest virus possible, because small viruses are simple. That's why Norman Salzman stopped working with vaccinia virus. But I looked at it in a different way. A small virus is not able to do much on its own. It relies almost completely on the cell, so you have to look not just at the small virus but also the cell. Vaccinia virus, in contrast, because it was a large virus, was able to do many more things on its own.

Early on, in fact the first year I was at NIH, it was discovered that poxviruses have the machinery in the virus particle for making RNA. Prior to that, it was thought that only the genetic material of the virus particle entered the cell. The poxvirus brings this transcriptional machinery as well as the genome into the cell, allowing it to replicate in the cytoplasm independently of the nucleus. That's what I really keyed onto. I decided to try to see what enzymes are packaged in the virus particle that enable it to make RNA. I thought that was a unique advantage, because the virus had already concentrated these enzymes for me in the particle, whereas cell biologists, in order to study RNA synthesis, had to start off with a whole cell.

I worked out conditions for extracting enzymes from virus particles. Two things helped me at the time. One was that I had a technician, Norman Cooper, who made virus for me continuously. He was always growing and purifying virus. I had, I'm sure, the largest amount of vaccinia virus that anyone has ever had. Then also I was joined by a postdoctoral fellow, Enzo Paoletti [Dr. Enzo Paoletti], who also was interested in the enzymes of the virus. We worked together side by side, really, in extracting and purifying enzymes. We purified essentially every enzyme in the virus particle. There are about a dozen of them.

Just at that period of time, it was shown that mRNA, messenger RNA in cells, has nucleotides that are modified by methylation. That's the addition of a methyl group onto the nucleic acid. I thought that if messenger RNA of cells is methylated, and the viral messenger RNA has to be translated in the cell, it should look like cell messenger RNA. Therefore, it should also be methylated. I had decided to try to test that idea.

Just at that time Aaron Shatkin, who had left NIAID several years before that, heard that a double-stranded RNA virus had methyl groups on its genomic RNA. We each decided to pursue this problem independently. I would investigate whether vaccinia mRNA is methylated. He would investigate whether reovirus mRNA, which is made by a double-stranded RNA virus, is methylated. They both can make RNA in a test tube, because they both have all the necessary enzymes packaged in the virus

particle. We both found that the mRNA in the viruses we studied was methylated, and we published that back to back. The hard part then was to determine the structure of the nucleotides that are methylated. I carried out that work in my lab with another postdoc, Cha Mer Wei [Dr. Cha Mer Wei].

The methylated nucleotides turned out to comprise a novel structure not previously described. There is a methyl group on a guanosine at the very end of the RNA, and then there is a 5'-to-5' triphosphate bond to the rest of the mRNA. That is unusual. It was unprecedented. Aaron Shatkin's lab also was investigating the structure in reovirus. We were not in communication about the structure, but we both determined it independently and then we submitted it at the same time. In addition to submitting the papers to the same journal, we sent the manuscripts to each other on the same day, thereby confirming that we had determined the same structure and showed that viral mRNA was "capped" with a methylated nucleotide.

That was in the '70s when I was doing mostly enzymology, mRNA synthesis, and the structure of messenger RNA. In the last half of the '70s, a number of events occurred. One was the advent of DNA sequencing by two different groups. Maxam and Gilbert [Drs. Allan Maxam and Walter Gilbert] at Harvard and Sanger [Dr. Frederick Sanger] at Cambridge both described ways of sequencing DNA. Also, with the discovery of restriction enzymes, work on recombinant DNA had started. These were game changers in the way research could be done. I realized that we had to incorporate these techniques to advance. With regard to recombinant DNA, I had another postdoc, Ricardo Wittek [Dr. Riccardo Wittek], from Switzerland. He also wanted to clone DNA. When he arrived, however, we were frustrated because the recombinant DNA guidelines for cloning DNA from a virus limited such work to safety conditions called BSL-4 [Bio-Safety Level 4], which was impossible to do because NIH did not have a BLS-4 laboratory available. However, several months later, new recombinant guidelines came out that would lower the required safety conditions to BSL-2, conditions which we could set up in our own lab.

Harden: This was clearly a transformative period in terms of what you could now do that you had not been able to do before. Before we move forward, however, I want to drop back and ask you about the influence of the Gordon Conferences in fostering new scientific ideas. Would you tell me a bit about them?

Moss: When I first started at NIH in 1966, these conferences on animal cells and viruses had just begun. These were small meetings, restricted at first to one hundred people. I think they may have gone up to 125. Every other year the main topics alternated between viruses and cells, because many of the cell biologists had gotten their start working with viruses. That was because there were better tools for working with viruses than for working with cells. The community who did molecular biology on viruses and cells was not much more than a hundred people at the time. These meetings really brought everyone together in a way that's impossible in this age. These were important meetings that I went to for many, many years. In fact, it was at a Gordon Conference meeting that the ability of poxviruses to make RNA was first described.

Harden: Also, towards the end of the '60s your group began working to understand how the antibiotic rifampicin inhibits viral synthesis. Would you talk a bit about that?

Moss: Yes. That was my first really exciting result. When I came to NIH, I had to learn to work with vaccinia virus. I was doing simple sorts of experiments, learning how to grow the virus, learning how to titer it, infecting cells, looking at the proteins made during all the periods of infection. These were details, really. Then a paper came out in *Nature*—two papers, actually—which described the fact that a drug, rifampicin, is able to inhibit the replication of vaccinia virus. Rifampicin was a known antibiotic that inhibits E. coli RNA polymerase.

One of the papers, which was written by a very prominent scientist, concluded that rifampicin was working the same way on vaccinia virus as on E. coli. It was preventing transcription. I thought this drug would be very useful for me since I was interested in gene expression. But when we started to work on it, I immediately saw that it did not affect transcription, and that the published experiments were flawed, and that it was working at a later step. At that point, I collaborated with an NCI

electron microscopist, Phil Grimley [Dr. Philip M. Grimley]. The pictures were amazing. The drug specifically interrupted a unique stage of assembly of the virus. It had nothing to do with gene expression. It had to do with the assembly mechanism. Although at that time it did not help me in my interest in gene expression, later on I used the drug to study assembly of viruses. That was really my first noteworthy result. We published it in *Nature* and follow ups in other journals.

Harden: Perhaps we can return to your description of how you began to use recombinant DNA for studying vaccinia. You had a really productive series of results.

Moss: Using recombinant DNA, we could take pieces of vaccinia DNA, put it into plasmids, grow it in E. coli, and sequence it. We were able to understand now the structure of the viral genome. We determined that the ends of the genome have unusual hairpin structures. We were also able to determine the sequences of genes and their putative regulatory sequences.

At that point, my work went in two directions, and the size of my lab doubled when that happened. One direction we took was to use all these tools to understand how poxviruses replicate. The other direction was to use vaccinia virus as a recombinant vector, because the new guidelines allowed me not only to clone DNA from a virus into bacteria, but allowed me to take pieces of DNA from another virus and insert them into the genome of vaccinia virus. Since vaccinia virus had been the virus used as the vaccine to eradicate smallpox [which is caused by a closely related poxvirus], the idea was that it might be possible to take a gene from another virus, say influenza virus, or hepatitis B virus, and later HIV, and put that gene into vaccinia virus, and use the reconstituted virus as a vaccine against one of these diseases. Now remember, I was working on gene expression, so I knew exactly how to put a gene from another virus into vaccinia virus so it would be expressed.

So, this direction of the work was to make vectors, put genes from other viruses into vaccinia, and see whether in fact we could express the proteins in order to characterize them and also to immunize animals. The idea would be that if we were now expressing a gene from influenza virus, then the animal would make an immune response to the encoded protein, and would provide protection. It did. We were able to show, for example, that if we put a hepatitis B gene into vaccinia virus and immunized chimpanzees with this altered virus, they would be protected against hepatitis B.

With that aspect of the work, I had a lot of collaborations both at NIH and outside. At NIH, there was Bryan Murphy [Dr. Bryan R. Murphy] in Bob Chanock's lab [Dr. Robert M. Chanock], Bob Purcell [Dr. Robert H. Purcell], Jay Berzofsky [Dr. Jay A. Berzofsky], and many others, because they had disease models, and we knew how to engineer the viruses. That work has led to animal veterinary vaccines that use that technology. There's a wild-life rabies vaccine that uses this technology.

There are also many, many human clinical trials with recombinant vaccinia viruses. We made recombinant viruses that are being tested by the army, universities, and some companies.

Harden: These are human vaccines?

Moss: Yes, there are human vaccines in phase one and two trials.

Harden: It must be very rewarding to you to realize that you have done this. You felt comfortable using vaccinia as the vector because it had been used for smallpox eradication and you knew that it was safe. Is this correct?

Moss: Not exactly. Although vaccinia virus was the virus used for the smallpox vaccine, it was not a good vaccine with regard to current safety standards. It caused lesions—

Harden: Yes, I have one.

Moss: —really big lesions. In someone who was immunodeficient, it could cause spreading disease. There was a lot of emphasis on making it a safer vaccine with these new recombinant vaccines. Around 1990—I'm not sure of the exact year—I had a postdoctoral fellow, Gerd Sutter [Dr. Gerd Sutter], who did his PhD thesis on a strain of vaccinia virus that could not replicate in human cells. It was called MVA. It had been passaged in chicken cells 500 times in order to make an attenuated smallpox vaccine, but very little was known about the basis for attenuation. Anyway, Gerd came to my lab and we started to study this virus. We showed that, remarkably, it was able to make as much protein as a replicating virus in human cells, but it couldn't spread to another cell. It was in between a live vaccine and a killed vaccine. It was a one round vaccine. If you inject it into somebody, it would infect cells and make the desired immunogen, and then it would disappear in a couple of days. MVA is the strain of vaccinia virus that is being tested mostly now in humans.

Harden: That is very interesting! In 1984, after Wally Rowe [Dr. Wallace P. Rowe] died in July 1983, you were asked to move over from the Laboratory of Biology of Viruses and become chief of the Laboratory Viral Diseases.

You have been there ever since. This is also the point at which you started to win all kinds of prizes. You were elected to the National Academy of Sciences. You must also have begun to do a lot more administration, overseeing other scientists, etc. I remember reading a comment from you that the most exciting time of your career was in the '70s when you were doing research at the bench. Would you talk about the pros and cons of transitioning to being lab chief?

Moss: Yes. If one is going to be a department head, which is what a lab chief is, essentially, the NIH is a good place. In 1984, when I became the chief, the lab was essentially reorganized. There was my section, the Macromolecular Biology Section. I was given the opportunity to recruit people, and my idea was to seek investigators that had a molecular biology emphasis in virology, and that's what I did. Mark Challberg [Dr. Mark Challberg] was the first person. He worked on herpes viruses. John Yewdell [Dr. John W. Yewdell] and Jack Bennink [Dr. John R. Bennink] were viral immunologists mainly studying influenza virus. Ed Berger [Dr. Edward A. Berger] worked on HIV entry into cells. Then Tom Kristie [Dr. Thomas M. Kristie], Alison McBride [Dr. Alison McBride], and Ted Pierson [Dr. Ted C. Pierson], working on herpesviruses, papilloma viruses and flaviviruses, respectively, were later recruits. We could communicate with each other, because we spoke the same molecular language but with different viruses.

You asked about the administrative load. There was a time where the paperwork at NIH appeared to be increasing logarithmically. When I first became lab chief, there wasn't very much paperwork. Then it increased, increased and increased with new rules and regulations for hiring, promoting, and evaluating staff; safety; and ordering equipment and supplies. Relief came when NIAID allowed each lab to hire a manager. That was really important, because it's become a full-time job. Now, Paul Kennedy [Mr. Paul E. Kennedy] is the administrator in our lab. He oversees an administrative staff. As lab chief, I didn't have nearly as much managerial work as I had before. I'm even happier to say that several months ago I passed on the lab chief position to Ted Pierson. Now, I am only responsible for my own section, the Genetic Engineering Section.

Harden: Let's return to the second direction in which your work went after you were able to do gene sequencing and work with recombinant DNA.

Moss: One direction, that I already discussed, was recombinant viruses as vaccines, and the other was to interrogate all the steps in the reproductive cycle of vaccinia virus. One way we did that was by developing novel ways to repress expression of individual genes. We could prevent a gene from making its protein, and then we could see what the consequence was. We could also isolate the gene, isolate the protein using the toolbox of modern molecular biology. Therefore, we explored every step in the lifecycle. We identified all the transcription factors and enzymes involved in RNA synthesis. We identified and analyzed all the proteins needed for the virus to enter into the cell, the proteins needed to replicate its DNA, its assembly, and how it assembles.

One of the most exciting things we've recently worked out is how the viral membrane is formed. That had been a question for fifty years, because viruses are thought to recruit their membranes from the cell, but electron microscopy did not reveal any connection between a poxvirus viral membrane and a cell membrane. I thought that the reason was because the connection might be too transient to capture by microscopy. So we looked at mutant viruses, and we found five different proteins that are required to recruit the viral membrane from the endoplasmic reticulum, a part of the cell. Remarkably, if the gene that codes for any one of these proteins is not expressed, you can see the connections between the viral membranes and the endoplasmic reticulum. This work was accomplished by several postdoctoral fellows and an expert electron microscopist, Andrea S. Weisberg [Ms. Andrea S. Weisberg], as well as colleagues at the Rocky Mountain Laboratories of NIAID.

We mainly concentrated on the genes that are required for replicating the virus, the essential genes. However, about half of the genes in poxviruses are not directly involved in making more virus. They're involved in preventing the cell from stopping their replication. In fact, in 1990 we described the first such protein in any virus. It was a protein that regulated complement action and prevented the host from killing the virus with complement. In the past several years, a major focus of my lab has switched to such proteins that are involved in interaction with the cell.

We're using many of the facilities the NIH provides. For example, there's a high throughput RNAi [RNA interference] facility that allows you to test every single human gene to see its role in the replication of the virus. We've worked out protocols to determine the roles of individual viral proteins. We also use the mass spectroscopy facility to identify protein interactions.

Harden: Would you comment, as we come to the end here, on the value of doing research and the intramural program as opposed, say, to being at a university?

Moss: I think an important feature of the intramural program is the way scientists are evaluated and funded. In the intramural program, we are rated on the work that we have accomplished over the past four years, which is easily verifiable. In contrast, the funding of university scientists is based on grant proposals, which are difficult to evaluate. There is both more flexibility in moving into new research areas and more stability in the intramural approach compared to the grant system. The intramural system has also provided continual support for excellent staff scientists including Pat Earl [Dr. Patricia L. Earl], Tania Koonin [Dr. Tania Koonin], and Linda Wyatt [Dr. Linda S. Wyatt], who have worked with me for many years. I've had opportunities to move to universities, but the NIH has been a continual attraction for me. I think my research has always been moving forward, and the support that I've gotten has been so terrific that I never wanted to interrupt it by moving someplace else. I have to commend the leaders of NIAID for maintaining such a productive workplace, one that's been free of political and other types of pressures. Tony Fauci [Dr. Anthony S. Fauci] has been the director at NIAID about as long as I've been lab chief at NIH.

Harden: We've reached the end of my questions. Is there anything else you would like to get on the record before we stop?

Moss: Just that I have had a rewarding career and hope to continue research as long as my health permits.

Harden: Thank you very much, Dr. Moss, for an excellent interview.